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Mumbai – 400 013

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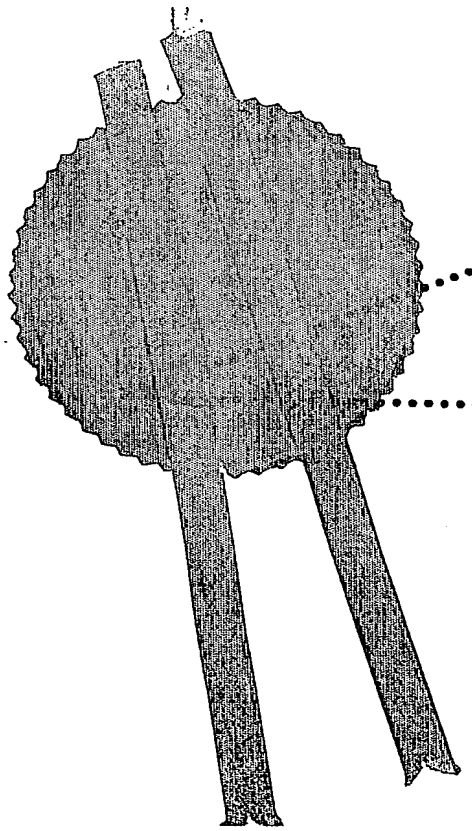
THE PATENTS ACT, 1970

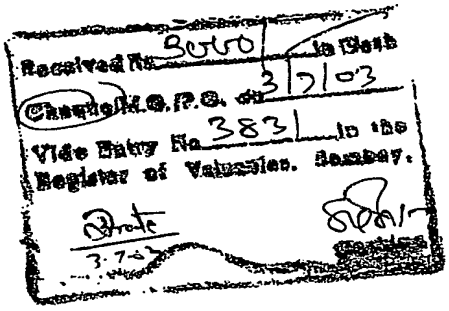
IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 03/07/2003 in respect of Patent Application No.676/MUM/2003 of M/S. CIPLA LIMITED, 289 BELLASIS ROAD, MUMBAI CENTRAL, MUMBAI – 400 008, STATE OF MAHARASHTRA, INDIA.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



Dated this 17th day of August 2004.

(R. BHATTACHARYA)
ASST.CONTROLLER OF PATENTS & DESIGNS.



FORM-1

THE PATENTS ACT, 1970

(39 OF 1970)

APPLICATION FOR GRANT OF PATENT

[See Section 5(2), 7, 54 and 135 and Rule 33A]

1. We,

   (a) **M/s. CIPLA LIMITED**

   (b) **289 BELLASIS ROAD, MUMBAI CENTRAL, MUMBAI – 400 008, THE STATE OF MAHARASHTRA, INDIA**

   (c) **NATIONALITY - INDIAN**

2. Hereby declare-

   (a) That we are in possession of an invention titled "**NOVEL PHARMACEUTICAL SYNTHESIS;**

   (b) That the **Provisional Specification** relating to this invention is filed with this application;

   (c) That there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention is:

   (a) **KANKAN, RAJENDRA NARAYANRAO**

   (b) **A-3/5, N. B. D. SOCIETY, N. S. S. ROAD, GHATKOPAR, MUMBAI – 400 084, MAHARASHTRA, INDIA**

   (c) **INDIAN CITIZEN**

   (a) **RAO, DHARMARAJ RAMCHANDRA**

   (b) **4/403, GARDEN ENCLAVE, POKHRAN ROAD 2, THANE (W), MUMBAI, MAHARASHTRA, INDIA**

   (c) **INDIAN CITIZEN**

(a) **NARAYAN, BHANU MANJUNATH**

(b) **103/SARITA CO-OP HSG SOCIETY, I.C.COLONY, BORIVLI (W), MUMBAI-400 103, MAHARASHTRA, INDIA**

(c) **INDIAN CITIZEN**

4. We, claim the priority from the application filed in convention countries, particulars of which are as follows:

Not Applicable

and declare that above application or each of the above applications was the first application(s) in a convention country/countries in respect of our invention.

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant:

Not Applicable

6. We state that the application is divided out of our application the particulars of which are given below and pray that this application deemed to have been filed on _____ under Section 16 of the Act.

Not Applicable

7. That we are the assignee of the true and first inventors.

8. That our address for service is as follows: -

LEX ORBIS
INTELLECTUAL PROPERTY ATTORNEYS
B-1/39, MALVIYA NAGAR
NEW DELHI – 110 017
TEL: 91 11 2667 1910; 2667 6075; 2667 3026
FAX: 91 11 2667 6077, 2667 3027
EMAIL: ipr@lexorbis.co.in

9. Following declaration was given by the inventor or applicant in convention country:

We are the true and first inventors for this invention declare that the applicant herein is our assignee.

Kankan, Rajendra Narayanrao
A-3/5, N. B. D. Society, N. S. S. Road, Ghatkopar, Mumbai – 400 084, Maharashtra, India
Indian Citizen

Rao, Dharmaraj Ramchandra
4/403, Garden Enclave, Pokhran Road 2, Thane (W), Mumbai, Maharashtra, India
Indian Citizen

Dr. Bhanu Manjunath Narayan
103/Sarita Co-Op Hsg Society, I.C.Colony, Borivli (W), Mumbai-400 103, Maharashtra, India
Indian Citizen

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application:
    a. Form 2 with the **PROVISIONAL SPECIFICATION** with abstract in triplicate; and
    b. Form 3 [Statement and Undertaking under Section 8];

c. Form 5 [Declaration as to Inventorship]

d. Payable at Par Cheque numbered 426751 to the tune of Rs. 3, 000/- drawn on the Standard Chartered Bank, New Delhi as Official Filing Fee.

We request that a patent may be granted to us for the said invention.

Dated this the 30th Day of June 2003

MANISHA SINGH
Agent for the Applicant
LEX ORBIS
Intellectual Property Attorneys
B-1/39[LGF], Malviya Nagar
New Delhi – 110 017

To

The Controller of Patents
The Patent Office
At Mumbai

FORM 2

The Patents Act, 1970

[39 of 1970]

PROVISIONAL SPECIFICATION

[See section 10]

1. **NOVEL PHARMACEUTICAL SYNTHESIS**

2. (a) **M/S. CIPLA LIMITED**
   (b) **289 BELLASIS ROAD, MUMBAI CENTRAL, MUMBAI – 400 008, INDIA**
   (c) **NATIONALITY – INDIAN**

The following specification describes the nature of this invention:

3. NOVEL PHARMACEUTICAL SYNTHESIS

[0001] Field of the Invention

[0002] In general, the present invention relates to pure polymorphic form 1 of Finasteride, 17β-(N-tert-butyl carbamoyl)-4-aza-5-alpha –androst-1-ene-3-one, improved processes for obtaining the pure polymorphic form 1 of Finasteride and pharmaceutical formulations thereof.

[0003] Background of the Invention

[0004] 5-alpha-reductase is an enzyme associated with the nuclear membrane and it is found in high concentrations in human male reproductive tissues, skin, and liver. It catalyzes the conversion of testosterone to dihydrotestosterone (DHT). Two isoenzymes (type I & type II) of 5-alpha-reductase have been identified in the human tissue. The type I isoenzyme is found in scalp skin, while the type II isoenzyme is found in the prostate. Type I 5-alpha-reductase is responsible for approximately one-third of the circulating DHT and type II 5-alpha-reductase is responsible for two-thirds of the circulating DHT. In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared to hairy scalp.

[0005] Finasteride is a potent inhibitor of the type II 5-alpha-reductase. Finasteride selectively blocks the production of dihydrotestosterone by a competitive inhibition of 5-alpha-reductase, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with 1 mg tablet.

[0006] Various prior art disclosures provide for different processes for producing and isolating pure polymorphic form I of Finasteride, 17β-(N-monosubstituted carbamoyl)-4-aza-5-alpha – androst-1-ene-3-one by using different organic solvents or mixture of protic and aprotic solvents.

[0007] The United States Patent numbered 4,760,071 to Rasmusson, et al. discloses a process for the preparation of 17.beta.-(N-monosubstituted carbamoyl)-4-aza-5.alpha.-androst-1-ene-3-one, pharmaceutical compositions used in inhibiting testosterone 5.alpha.-reductase and methods of treating hyperandrogenic conditions with the compound, particularly benign prostatic hypertrophy.

[0008] The United States Patent numbered 5,652,365 to McCauley, et al. discloses a process for producing polymorphic Form I of Finasteride, 17B-(N-tert-butyl carbamoyl)-4-aza-5-alpha.-androst-1-ene-3-one. The process disclosed in this patent, polymorphic Form I of Finasteride is produced by crystallizing a solution of Finasteride in a water immiscible organic solvent and 0% or more by weight of water, producing solvated and non-solvated Finasteride in solution. In accordance with this process, the amount of organic solvent and water in the solution is sufficient to cause the solubility of the non-solvated form of Finasteride to be exceeded. The non-solvated form of Finasteride is less soluble than any other form of Finasteride in the organic solvent and water solution. The process involves recovering the resultant solid phase and removing the solvent. In the process disclosed the water immiscible organic solvent is ethyl acetate or isopropyl acetate and the amount of water in the solvent mixture is below 4 mg./ml.

[0009] The United States Patent numbered 5,886,184 to Dolling, et al. discloses a process for producing Finasteride, the process involving reacting the magnesium halide salt of 17-beta.-carboalkoxy-4-aza-5-alpha.-androst-1-ene-3-one with t-butylamino magnesium halide, present in at least a 2:1 molar ratio to the ester, formed from t-butyl

amine and an aliphatic/aryl magnesium halide at ambient temperature in an inert organic solvent under an inert atmosphere followed by heating and recovering the product Finasteride polymorphic crystalline Forms I and II.

[0010] The United States Patent Application numbered 20020042425A1 to Gormely, Glenn J.; et al. discloses an invention that involves a method of treating and/or reversing androgenic alopecia and promoting hair growth, and methods of treating acne vulgaris, seborrhea, and female hirsutism, by administering to a patient in need of such treatment a 5-alpha.-reductase 2 inhibiter, such as Finasteride, in a dosage amount under 5mgs/day. This invention discloses the process for producing Finasteride polymorphic form by using solvents like glacial acetic acid.

[0011] The United States Patent numbered 5,670,643 to Davis, et al. discloses a method of preparing Finasteride by reacting the acid chloride with t-butylamine in an aprotic solvent, e.g., pyridine, toluene, methylene chloride, dimethylformamide, or acetonitrile in the presence of a base, e.g., pyridine, diisopropylethylamine, dimethylaminopyridine, or triethylamine, in the temperature range of from about 20.degree C to about 60 degree C. Salts such as LiCl and LiBr, might be used to facilitate this reaction. The resulting compound may be purified by standard methods of the art such as chromatography and crystallization.

[0012] The European Patent Application numbered 93203163.6 to Merck & Co. discloses a new process for producing Finasteride, the process involving reacting magnesium halide salt of 17beta-carboaloxy-4aza-5 alpha androst-1-en-3-one with t- butylamino magnesium halide, present in at least a 2:1 molar ratio to the ester, formed from t-butyl amine and an aliphatic /aryl magnesium halide at ambient temperature in a inert organic solvent under an inert atmosphere followed by heating and recovering the product Finasteride. Also disclosed in this patent are

the two polymorphic forms I and II of Finasteride and the processes for their production.

[0013] There are several disadvantages associated with the known methods for obtaining pure polymorphic form 1 of Finasteride. In the known methods the polymorphic form 1 of Finasteride is obtained from solvents or mixtures of solvents like tetrahydrofuran, glacial acetic acid, ethyl acetate, toluene and/or isopropyl acetate. Typically one of the principal disadvantages in the prior art processes is that during the drying step solvents are difficult to be removed from the crystals and pure crystals are therefore not obtained. The other disadvantage with the prior art processes is that they require too many controls, which make them unsuitable for industrial production.

[0014] It is therefore important and essential to develop a process for obtaining pure polymorphic form 1 of Finasteride wherein the process is devoid of the disadvantages mentioned above.

[0015] Summary of the Invention

[0016] In accordance with the principal aspect of the present invention, herein disclosed is a pure polymorphic form 1 of Finasteride, 17β-(N-tert-butyl carbamoyl)-4-aza-5-alpha –androst-1-ene-3-one.

[0017] In accordance with another principal aspect of the present invention, an improved process for obtaining pure polymorphic form 1 of Finasteride, 17β-(N-tert-butyl carbamoyl)-4-aza-5-alpha –androst-1-ene-3-one has been devised, wherein the process comprises crystallizing Finasteride by replacing solvent with a non-solvent. The invention herein disclosed does not address processes for producing Finasteride. The invention employs known processes to produce Finasteride. The Finasteride thus produced is crystallized in the manner described herein to obtain its pure polymorphic form 1.

[0018] In accordance with another aspect, the present invention provides for an improved process for obtaining polymorphic form I of Finasteride by using aqueous medium as non-solvent, thus avoiding the difficulty to remove the solvent traces from the product during the drying process.

[0019] In accordance with yet another aspect, the present invention provides for an improved process for producing polymorphic form I of Finasteride by replacing solvent to non-solvent during distillation wherein the preferred non-solvent is an organic solvent, the preferred solubility of Finasteride is less than 1 in 20 parts of the solvent at its boiling point and non-solvent may be straight chain or branched alkanes like hexane, heptane or octane, or aromatic solvents like toluene, xylene or esters such as isobutyl acetate or isopropyl acetate.

[0020] In accordance with still another aspect, the present invention provides for an improved process for obtaining polymorphic form I of Finasteride, wherein the process is suitable for large scale manufacture and does not have too many controls, the residue of solvents in the crystals is very low and the crystals obtained are free flowing and suitable for converting to dosage forms directly or after micronization.

[0021] In accordance with another principal aspect, the present invention provides for an improved process for producing polymorphic form I of Finasteride, wherein the process comprises replacing solvent to non-solvent at the time of distillation, having higher boiling point as compared to the solvent. The solvent is distilled off either at atmospheric pressure or under reduced pressure and adding the non-solvent into the reactor either in parts or continuously in a slow stream. The non-solvent may be such that it may be miscible or immiscible with the solvent.

[0022] In accordance with still one another aspect, the present invention discloses pharmaceutical formulations comprising the isolated pure polymorphic form I of Finasteride. The formulation further comprises intra granular ingredients, binders, extragranular agents and a coating agent.

[0023] In accordance with yet another aspect there are provided oral dosage forms of a pharmaceutical formulation selected from the group consisting of tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions. The pharmaceutical formulation comprises isolated pure polymorphic form I of Finasteride. The formulation preferably comprises a potency equivalent to 1 mg to 500 mg of Finasteride.

[0024] Detail Description of the Invention

[0025] In the preferred embodiment, herein disclosed is a process for producing 5-alpha-reductase inhibitor, in particular polymorphic form I of Finasteride in which Finasteride is first dissolved in a solvent such as methanol or dichloromethane. The dissolution may be done at ambient or at reflux temperature or any temperature in between. The solution of Finasteride in the solvent may optionally be clarified by using decolorizing agents. The solvent is then distilled off partially and a non-solvent is introduced. The non-solvent in the context of this invention is aqueous medium wherein the medium is water.

[0026] In another preferred embodiment, herein disclosed is a process for producing 5-alpha-reductase inhibitor, in particular polymorphic form I of Finasteride in which Finasteride is first dissolved in a solvent such as methanol or dichloromethane. The dissolution may be done at ambient or at reflux temperature or any temperature in between. The solution of Finasteride in the solvent may optionally be

clarified by using decolorizing agents. The solvent is then distilled off partially and a non-solvent is introduced. The non-solvent in the context of this invention may be construed as any organic solvent in which the solubility of Finasteride is not more than 5% w/v or 1 in 20 at its boiling point, or water. The organic non-solvent may be selected from straight chain or branched alkanes like hexane, heptane or octane, or aromatic solvents like toluene, xylene or esters such as isobutyl acetate, isopropyl acetate.

[0027] In still another preferred embodiment, the present invention is addressed at a process comprising, replacing the solvent partially or completely by the non-solvent, preferably completely. Then stirring the precipitated product in the non-solvent for a period sufficient to transform the product to form I.

[0028] In still another preferred embodiment, the present invention is addressed at a process for preparing Finasteride tablets for oral administration, which tablets are film-coated tablets containing 1 mg or 5 mg of finasteride. Conventional method has been used in mixing with following inactive ingredients like intra-granular ingredients which are lactose monohydrate, sodium starch glycolate, starch, binder which are starch (for spray), lactose monohydrate (for spray), purified water, extra-granular ingredients which are colloidal silicon dioxide, docusate sodium benzoate, sodium starch glycolate, magnesium stearate and coating the tablet by using coating agents such as opadry 04F50702 blue and purified water.

[0029] The present invention is illustrated below with reference to the following examples:

Example 1

[0030] Dichloromethane, 150 lit and Finasteride 11 kg are charged to a reactor and stirred to dissolve. Dichloromethane is distilled

out and water 120 lit is added and the distillation is continued till the vapour temperature reaches about 80 C. The contents are cooled to ambient and stirred for 24-30 hrs and the product is filtered and washed with water and dried under vacuum to obtain Finasteride Form I having purity about 99.7%.

Example 2

[0031] Methanol, 170 lit and Finasteride 10 kg are charged to a reactor, 1 kg neutral alumina and 1 kg activated charcoal are added and stirred for 15 min. at temp 25-35°C and filtered. The filtrate is transferred to another reactor and methanol is distilled out till thick slurry is obtained. Toluene 70 lit is added and the distillation is continued till the vapour temperature reaches about 110°C. The contents are cooled to ambient and stirred for 4-5 hrs and the product is filtered and washed with toluene and dried under vacuum to obtain Finasteride Form I having purity 99.8%.

Example 3

[0032] Dichloromethane, 150 lit and Finasteride 11 kg are charged to a reactor.1 kg neutral alumina and 1 kg activated charcoal are added and stirred for 15 min. at temp 25-35°C and filtered. The filtrate is transferred to another reactor and Dichloromethane is distilled out till thick slurry is obtained. Isopropyl acetate 80 lit is added and the distillation is continued till the vapour temperature reaches about 80°C. The product is filtered hot and washed with isopropyl acetate and dried under vacuum at 80°C to obtain Finasteride Form I having purity 99.8%.

Example 4

[0033] Table for Pharmaceutical Formulation:

Sl. No.	Name of ingredients	Qty/tab(mg)
INTRAGRANULAR		
1.	Finasteride USP	5.00

2.	Lactose monohydrate	79.45
3.	Sodium starch Glycolate	10.00
4.	Starch	35.00
BINDER		
5.	Starch (For spray)	0.80
6.	Lactose monohydrate (For spray)	12.00
7.	Purified water	q.s.
EXTRAGRANULAR		
8.	Colloidal Silicon dioxide	1.50
9.	Sodium starch Glycolate	5.00
10.	Docusate sodium benzoate	0.50
11.	Magnesium stearate	0.75
Tablet weight		**150.00**
COATING		
12.	Opadry 04F50702 blue	5.00
13.	Purified water	q.s.
Total		**155.00**

[0034] Certain modifications and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.

DATED THIS THE 30TH DAY OF JUNE 2003

Manish Singh
AGENT FOR THE APPLICANT
LEX ORBIS
INTELLECTUAL PROPERTY
ATTORNEYS
B-1/39, MALVIYA NAGAR
NEW DELHI - 110 017

4. NOVEL PHARMACEUTICAL SYNTHESIS

ABSTRACT

An improved process for obtaining pure polymorphic form 1 of Finasteride, 17β-(N-tert-butyl carbamoyl)-4-aza-5-alpha–androst-1-ene-3-one and pharmaceutical formulations comprising the same has been disclosed. Also disclosed is the pure polymorphic form 1 of Finasteride thus obtained. Pharmaceutical formulation comprising the pure polymorphic form 1 of Finasteride thus obtained and dosage forms thereof have been disclosed.